

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1, 10, 12, 13 and 21 in the reply filed on 04/17/2008 is acknowledged.

Claims 2-9, 11 and 14-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/17/2008.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the last panel in figure 7 contains an error. The horizontal axis is labeled in two places with "Braak 4-8". This should be "Braak 4-6". Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one

Art Unit: 1637

figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may **NOT** be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 12, 13 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

Art Unit: 1637

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to diagnosing/prognosticating neurodegenerative disease, or predicting risk of developing said disease, inclusive of Alzheimer’s disease (AD). The invention is the class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are drawn to *any* subject (human or otherwise), *any* neurodegenerative disease (with some claims specifically limited to AD), and furthermore to *any* sample of said subject. This is in contrast to the data presented in Applicant’s disclosure, which are asserted to show an increase in SPGL1 mRNA levels in certain areas of the brain in human subjects with AD as compared to unaffected human subjects. In contrast, other areas of the brain showed similar levels between the

two groups. Hence, the disclosure clearly does not enable the methods for the myriad of sample types discussed at page 13, line 14 of the specification as filed (e.g. cerebrospinal fluid, saliva, urine, serum, plasma, blood, mucus).

There are no data presented whatsoever for any other neurodegenerative disease. Thus, the disclosure clearly does not enable diagnosis, prognostication or prediction of any of the multiple diseases discussed at page 10, line 1 of the specification as filed (e.g. Parkinson's disease, Huntington's disease, ALS, Pick's disease, age-related macular degeneration, narcolepsy, prion disease, "mild-cognitive impairment", among several others mentioned).

Furthermore, claim 1 encompasses (and claims 10, 12, 13 and 21 require) practicing the method by measuring the SPGL1 protein level or activity, whereas the only data comparing AD subjects with control subjects are assessments of mRNA levels. While there are experiments detecting SPGL1 protein in cell extract or intact cells, these are cell lines engineered to express SPGL1. Thus Applicant was clearly in possession of the antibody and brain tissue samples from AD and control subjects, but discloses no experimental data using the antibody to detect SPGL1 in these tissue samples.

Quantity of Experimentation

To practice claim 1 to the full extent of its scope would require an enormous amount of further experimentation, and may not be possible given *any* amount of further experimentation, since, for example, there has been no established correlation of SPGL1 level/activity with any neurodegenerative diseases (other than the presumptive

one asserted by Applicant for AD). Thus, one would have to conduct extensive clinical trials to determine whether any neurodegenerative disease was correlated with SPGL1. Even in the case of AD, the data presented in the disclosure do not justify Applicant's conclusion at page 13, line 4: "Consequently, the SGPL1 gene and its corresponding transcription and/or translation products have a causative role in the regional selective neuronal degeneration typically observed in AD."

The unpredictability of the art and the state of the prior art

With regard to predicting etiology of diseases, it cannot be predicted even today whether a particular disease is caused by the dysregulation of a particular gene or protein; such a correlation can only be established by experimentation. With regard to AD, which is the only neurodegenerative disease for which the disclosure provides any experimental data, Applicant's statement at page 2, line 19 of the specification as filed is relevant: "Currently, there is no cure for AD, nor is there an effective treatment to halt the progression of AD or even to diagnose AD ante-mortem with high probability." Likewise at page 2, line 29: "Although there are rare examples of early-onset AD which have been attributed to genetic defects in the genes for amyloid precursor protein (APP), presenilin-1 and presenilin-2, the prevalent form of late-onset sporadic AD is of hitherto unknown etiologic origin."

As stated at page 2, line 25 (citations omitted): "Efforts to detect further susceptibility genes and disease-linked polymorphisms lead to the assumption that specific regions and genes on human chromosomes 10 and 12 may be associated with late-onset AD." Evidently, SPGL1 gene is found on chromosome 10, as discussed by

Art Unit: 1637

Applicant at page 3, line 10 (citations omitted): “The human SGPL1 cDNA, as referred to in the present invention, was cloned and the corresponding SGPL1 gene was mapped within the AD hot spot region of chromosome 10q (10q22).” However, this alone does not suffice to prove any correlation between SPGL1 and AD; as indicated by the information obtained from NCBI (see printout accompanying this Office action), the 3 segments of 10q22 span 11 million base pairs and comprise 128 genes.

Additionally, claim 1 encompasses (and claims 10, 12, 13 and 21 require) practicing the method by measuring the SPGL1 protein level or activity, whereas the only data comparing AD subjects with control subjects are assessments of mRNA levels. Even assuming the data disclosed reflects a statistically significant difference in the level of SPGL1 mRNA between AD and control subjects (see examiner’s argument to the contrary under *Working Examples* below), the art teaches that levels of mRNA do not always correlate with levels of protein. For example, Holt et al (Current Opinion in Biotechnology, 11(5):445-9, October 2000) teach: “Changes in mRNA levels do not, however, necessarily reflect changes in the level of the corresponding protein because of different rates of protein translation and degradation” (page 447, column 1, 1st paragraph). Similarly, Banks et al (Lancet, 356(9243):1749-56, November 2000) teach: “The expression or function of proteins is modulated at many points from transcription to post-translation (figure 1), which generally cannot be predicted from analysis of nucleic acids alone. There is poor correlation between the abundance of mRNA transcribed from the DNA and the respective proteins translated from that mRNA” (page 1750, column 1, 1st paragraph).

The art also indicates that gene association studies are highly unpredictable and often unrepeatable. In fact, Lucentini (The Scientist 18(24):20; 2004) titled his article "Gene Association Studies Typically Wrong" and states: "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding" (see page 2 of printout). Moonesinghe et al (PNAS 105(2):617-622 (2008)) observe (see abstract): "Many gene–disease associations proposed to date have not been consistently replicated across different populations. Nonreplication often reflects false positives in the original claims."

Working Examples

There is a working example in the disclosure comparing levels of SPGL1 mRNA in various brain tissues from AD and control subjects, as shown in figures 7-9 and discussed on pages 28-29 of the specification as filed. This example makes use of the term Braak stage, which is explained on 9 of the specification as a system of grading the state of progression of AD, with 0-2 representing healthy controls, and 4-6 representing AD subjects.

Figure 7 is described on page 28 as a comparison using statistical method of the median at 98% confidence level. To the extent that the vertical lines in the graph shown in figure 7 represent the 98% confidence interval, it is noted that in all cases, these confidence levels overlap. This is generally considered to indicate there is no statistically significant difference between the groups being compared. For example, Kammer et al (Urol Res 21:227-233; 1993) state on page 228 (*Statistical analysis*):

“Close inspection of the data revealed that they did not follow a Gaussian distribution.

Therefore for a comparison of the concentrations of PSA and PSP9, in the sera of the three groups, the corresponding median and the respective 95 % and 99% confidence intervals were introduced in accordance with a previously published procedure [22].

Confidence ranges of median values for disease groups that did not overlap with those of the control group were considered to be significantly different” (emphasis provided).

The obvious corollary to this statement would be that if the confidence intervals *did* overlap (as is the case in Applicant’s figure 7), then the median values would *not* be considered significantly different. It is noted that the lead author on this article is H. von der Kammer, and presumably is the same Heinz von der Kammer as one of the inventors listed on the instant application.

Figure 8, as described on page 28, represents data from 15 AD patients and 25 controls, while figure 9 represents data from six AD patients and three controls. These samples are far too small to establish a significant correlation. Moonesinghe et al observe (see first paragraph of *Discussion*, page 620): “Replication sample sizes have gradually increased to exceed 40,000 subjects in some studies (14, 30). Our calculations suggest that such sample sizes or even larger are absolutely essential in generating sufficient power that a proposed association of small or modest effect size can be properly replicated, at least when between-study heterogeneity is not large.”

Guidance in the Specification.

There is guidance in the specification as to how to practice the claimed invention. What is lacking is any reasonable certainty that one would in fact be able to successfully

Art Unit: 1637

diagnose, prognosticate, or predict risk of AD, much less *any* neurodegenerative disease, by practicing the claimed method.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Due to the unpredictability in the art, the claims are not enabled with respect to any neurodegenerative disease. Furthermore, even with regard to Alzheimer's disease, the small sample size and overlapping confidence intervals do not support Applicant's conclusion of a correlation between SPGL1 level/activity and AD, and therefore even for AD the claims are not enabled by the disclosure.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1637

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637